

REMARKS

Claims 1 -12 remain in the application and all stand rejected for various reasons discussed below.

REJECTION OF CLAIMS 1 - 12 UNDER 35 USC 112, FIRST PARAGRAPH

The claims stand rejected under 35 USC 112, first paragraph, because the Office finds that the specification does not provide the necessary guidance for the term "preventing." The applicants recognize that in some instances it would not be possible to "prevent" some of the conditions encompassed within the term "other bone diseases." For example, it would not be possible with the claimed method to "prevent" broken bones. Rather the use of the term "prevent" as used within the claims was intended to relate to the prevention of bone loss associated with some of the claimed conditions and not necessarily with prevention per se of the conditions itself and thus is not distinguishable from "treatment" of such conditions. Thus applicants have amended the claim language to remove the objectionable term "prevent." This rejection is thus considered moot.

REJECTION OF CLAIMS 1 - 12 UNDER 35 USC 112, SECOND PARAGRAPH

The claims have also been rejected under 35 USC 112, second paragraph, because the Office finds that the term "other bone disease" is not *ipsis verbis* defined in the specification. Applicants submit that the term is defined at page 3, lines 4 - 15 and that *ipsis verbis* definition is not required. Nevertheless, applicants, at this time, would like to focus the Office's attention on the treatment of osteoporosis and bone resorption and thus applicants have amended the claims by removing reference to treatment of "other bone disease." Applicants reserve the right to file a continuation application directed to the now deleted subject matter. This rejection is considered moot in view of these amendments to the claims.

REJECTION OF CLAIMS 1 - 6 UNDER 35 USC 103(A) OVER BATTS ET AL.

The Office has rejected claims 1 - 6 under 35 USC 103(a) over Batts et al. The Office states that Batts et al. discloses that the instant compounds are useful in methods for treating arthritis. The Office further states, without authority, that arthritis is known to be associated with bone loss,



and thus concludes that it would have been obvious to use the instant compounds to treat osteoporosis and bone resorption. Applicants disagree for several reasons.

Batts et al. discloses the use of 6 specific oxazolidinones for the treatment of arthritis. None of the 6 disclosed oxazolidinones are thioamide oxazolidinones as described in this application. The Office provides no reason to expect that substituting a thioamide group in the compounds of Batts et al. would be expected to produce compounds having the ability to treat arthritis, let alone osteoporosis and bone resorption.

Applicants further disagree with the Office's position that arthritis is known to be associated with bone destruction. Clearly, Batts et al. uses the term arthritis in the context of a disease with inflammatory basis not in the context of a disease associated with bone loss. Applicants submit that clearly one of ordinary skill in the art upon reading the disclosure of Batts et al. would recognize that the treatment set forth in this reference relates to the treatment of arthritis having an inflammatory basis and that there would be no reason to expect that the compounds disclosed in Batts, et al. could be useful in treating other conditions, not inflammatory in basis, such as the instantly claimed methods of treating osteoporosis and bone resorption. For these reasons, applicants submit that it would not have been obvious to one of ordinary skill in the art to modify the compounds of Batts et al. and have the expectation that the modified compounds would possess the different and useful properties claimed herein.

REJECTION OF CLAIMS 1 - 6 UNDER 35 USC 103(A) OVER HESTER ET AL. IN VIEW OF NAIR ET AL. AND THE REJECTION OF CLAIMS 7 - 12 UNDER 35 USC 103(A) OVER YOSHIDA ET AL. IN VIEW OF NAIR ET AL.

The Office has rejected claims 1 - 6 under 35 USC 103(a) over Hester et al. in view of Nair et al. The Office finds that Hester et al. discloses the antibacterial activity of the compounds of this invention and that Nair et al. discloses that certain bacterial infections are associated with bone loss. The Office concludes that it would have been obvious to treat bone loss associated with the compounds of this invention.

The Office has further rejected claims 7 - 12 under 35 USC 103(a) over Yoshida et al. in view of Nair et al. The Office finds that Yoshida et al. describes that certain compounds within the instant claims have antibacterial activity and that together with Nair et al. suggest the use of these compounds to treat bone loss associated with bacterial infections.

Applicants have previously stated that such rejections are based on the premise that the compounds, by treating a bone destroying infection would prevent bone loss, but that it was not known that bone formation could be promoted, as distinguished from loss prevention, by treatment with these compounds. Applicants submit thus that Hester et al and Yoshida et al. in view of Nair et al do not render obvious the treatment previously claimed in this application. Nevertheless, as mentioned above, applicants have amended the claims to delete the treatment of "other bone disease" including bacterially induced bone loss diseases, and thus applicants submit that this rejection is moot. Such rejection will be addressed in a subsequent continuation application should applicants decide to pursue this course of action.

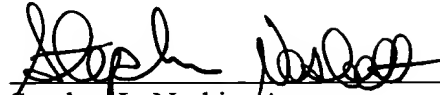
CONCLUDING REMARKS

Applicants submit that the rejection under 35 USC 112, first paragraph, has been overcome by amendment of the claims to delete the term "preventing." The rejection under 35 USC 112, second paragraph, has likewise been overcome by deletion of the phrase "other bone diseases." Applicants submit that these rejections should be withdrawn in view of these amendments.

Applicants further submit that the rejections under 35 USC 103(a) of claims 1 - 6 and 7 - 12, have been overcome by the deletion of the term "other bone diseases" and that these rejections should be reconsidered in view of applicants' remarks above and in view of this claim amendment.

Applicants submit that the claims as amended are clearly allowable. Applicants therefore respectfully request withdrawal of the outstanding rejections and await an early allowance of the claims of this application.

Respectfully submitted,



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Dated: 3/28/03

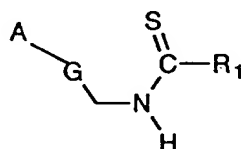
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Version with markings to show changes made

In the claims:

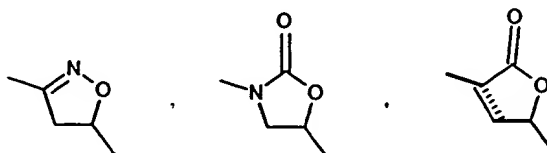
1 (Twice Amended) A method of treating [or preventing] osteoporosis[,] or bone resorption[, or other bone disease characterized by the need to enhance bone formation] in a vertebrate mammal in need thereof comprising the administering to the vertebrate mammal an effective amount of a compound of formula I



I

or pharmaceutical acceptable salts thereof wherein:

G is

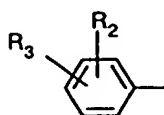


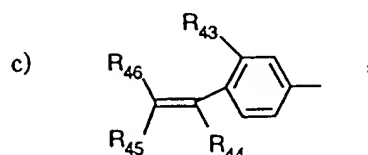
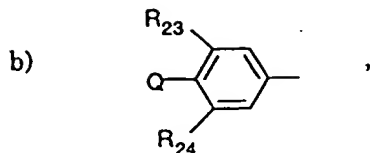
R₁ is

- a) H,
- b) NH₂,
- c) NH-C₁₋₄ alkyl,
- d) C₁₋₄ alkyl,
- e) -OC₁₋₄ alkyl,
- f) -S C₁₋₄ alkyl,
- g) C₁₋₄ alkyl substituted with 1-3 F, 1-2 Cl, CN or -COOC₁₋₄ alkyl,
- h) C₃₋₆ cycloalkyl,
- i) N(C₁₋₄ alkyl)₂ or
- j) N(CH₂)₂₋₅;

A is

a)

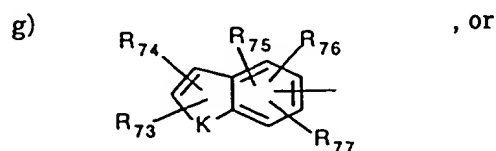




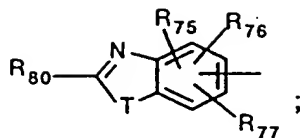
- d) a 5-membered heteroaromatic moiety having one to three atoms selected from the group consisting of S, N, and O, wherein the 5-membered heteroaromatic moiety is bonded via a carbon atom, wherein the 5-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring, wherein the heteroaromatic moiety is optionally substituted with one to three R₄₈,

- e) a 6-membered heteroaromatic moiety having at least one nitrogen atom, wherein the heteroaromatic moiety is bonded via a carbon atom, wherein the 6-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring, wherein the heteroaromatic moiety is optionally substituted with one to three R₅₅,

- f) a β -carbolin-3-yl, or indolizinyI bonded via the 6-membered ring, optionally substituted with one to three R₅₅,



h)

wherein R_2 is

- a) H,
- b) F,
- c) Cl,
- d) Br,
- e) C_{1-3} alkyl,
- f) NO_2 , or
- g) R_2 and R_3 taken together are $-O-(CH_2)_h-O-$;

 R_3 is

- a) $-S(=O)_i R_4$,
- b) $-S(=O)_2-N=S(O)_j R_5 R_6$,
- c) $-SC(=O)R_7$,
- d) $-C(=O)R_8$,
- e) $-C(=O)R_9$,
- f) $-C(=O)NR_{10}R_{11}$,
- g) $-C(=NR_{12})R_8$,
- h) $-C(R_9)(R_{11})-OR_{13}$,
- i) $-C(R_9)(R_{11})-OR_{13}$,
- j) $-C(R_9)(R_{11})-OC(=O)R_{13}$,
- k) $-C(R_9)(R_{11})-OC(=O)R_{13}$,
- l) $-NR_{10}R_{11}$,
- m) $-N(R_{10})-C(=O)R_7$,
- n) $-N(R_{10})-S(=O)_i R_7$,
- o) $-C(OR_{14})(OR_{15})R_8$,
- p) $-C(R_9)(R_{16})-NR_{10}R_{11}$, or
- q) C_{1-8} alkyl substituted with one or more $=O$ other than at alpha position, $-S(=O)_i R_{17}$, $-NR_{10}R_{11}$, C_{2-5} alkenyl, or C_{2-5} alkynyl;

 R_4 is

- a) C_{1-4} alkyl optionally substituted with one or more halos, OH, CN, $NR_{10}R_{11}$, or $-CO_2R_{13}$,
- b) C_{2-4} alkenyl,

- c) $-NR_{16}R_{18}$,
- d) $-N_3$,
- e) $-NHC(=O)R_7$,
- f) $-NR_{20}C(=O)R_7$,
- g) $-N(R_{19})_2$,
- h) $-NR_{16}R_{19}$, or
- i) $-NR_{19}R_{20}$,

R_5 and R_6 at each occurrence are the same or different and are

- a) C_{1-2} alkyl, or
- b) R_5 and R_6 taken together are $-(CH_2)_k$;

R_7 is C_{1-4} alkyl optionally substituted with one or more halos;

R_8 is

- a) H, or
- b) C_{1-8} alkyl optionally substituted with one or more halos, or C_{3-8} cycloalkyl;

R_9 is C_{1-4} alkyl substituted with one or more

- a) $-S(=O)R_{17}$,
- b) $-OR_{13}$,
- c) $-OC(=O)R_{13}$,
- d) $-NR_{10}R_{11}$, or
- e) C_{1-5} alkenyl optionally substituted with CHO;

R_{10} and R_{11} at each occurrence are the same or different and are

- a) H,
- b) C_{1-4} alkyl, or
- c) C_{3-8} cycloalkyl;

R_{12} is

- a) $-NR_{10}R_{11}$,
- b) $-OR_{10}$; or
- c) $-NHC(=O)R_{10}$;

R_{13} is

- a) H, or
- b) C_{1-4} alkyl;

R_{14} and R_{15} at each occurrence are the same or different and are

- a) C_{1-4} alkyl, or
- b) R_{14} and R_{15} taken together are $-(CH)_l$;

R₁₆ is

- a) H,
- b) C₁₋₄ alkyl, or
- c) C₃₋₈ cycloalkyl;

R₁₇ is

- a) C₁₋₄ alkyl, or
- b) C₃₋₈ cycloalkyl;

R₁₈ is

- a) H,
- b) C₁₋₄ alkyl,
- c) C₂₋₄ alkenyl,
- d) C₃₋₄ cycloalkyl,
- e) -OR₁₃ or
- f) -NR₂₁R₂₂;

R₁₉ is

- a) Cl,
- b) Br, or
- c) I;

R₂₀ is a physiologically acceptable cation;

R₂₁ and R₂₂ at each occurrence are the same or different and are

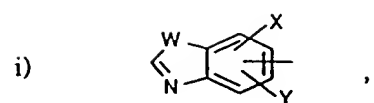
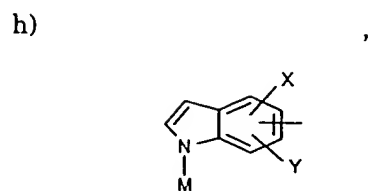
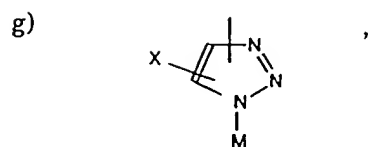
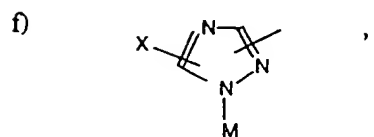
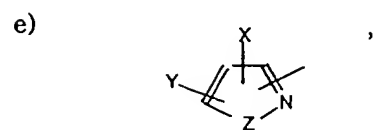
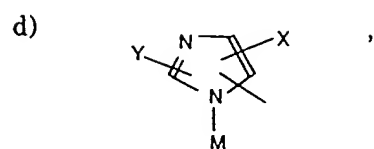
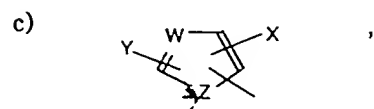
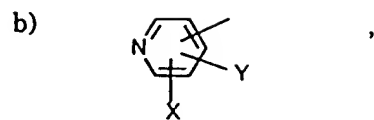
- a) H,
- b) C₁₋₄ alkyl, or
- c) -NR₂₁R₂₂ taken together are -(CH₂)_m-;

wherein R₂₃ and R₂₄ at each occurrence are the same or different and are

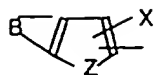
- a) H,
- b) F,
- c) Cl,
- d) C₁₋₂ alkyl,
- e) CN
- f) OH,
- g) C₁₋₂ alkoxy,
- h) nitro, or
- i) amino;

Q is

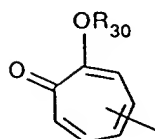




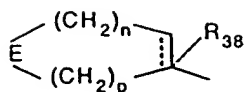
j)



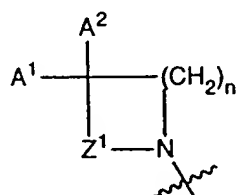
k)



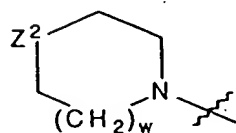
l)



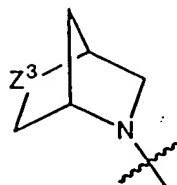
- m) a diazinyl group optionally substituted with X and Y,
- n) a triazinyl group optionally substituted with X and Y,
- o) a quinolinyl group optionally substituted with X and Y,
- p) a quinoxalinyl group optionally substituted with X and Y,
- q) a naphthyridinyl group optionally substituted with X and Y,
- r)



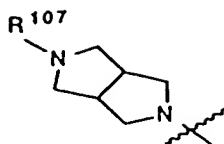
s)



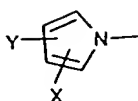
t)



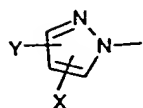
u)



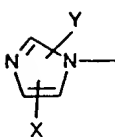
v)



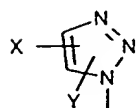
w)



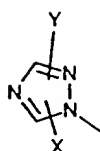
x)



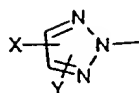
y)



z)

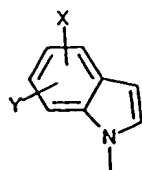


aa)

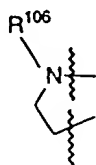


bb)

or,



Q and R₂₄ taken together are



wherein Z¹ is

- a) -CH₂-,
- b) -CH(R¹⁰⁴)-CH₂-,
- c) -C(O)-, or
- d) -CH₂CH₂CH₂-;

wherein Z² is

- a) -O₂S-,
- b) -O-,
- c) -N(R¹⁰⁷)-,
- d) -OS-, or
- e) -S-;

wherein Z³ is

- a) -O₂S-,
- b) -O-,
- c) -OS-, or
- d) -S-;

wherein A¹ is


- a) H-, or
- b) CH₃;

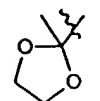
wherein A² is

- a) H-,
- b) HO-,
- c) CH₃-,
- d) CH₃O-,
- e) R¹⁰²O-CH₂-C(O)-NH-
- f) R¹⁰³O-C(O)-NH-,
- g) (C₁-C₂)alkyl-O-C(O)-,
- h) HO-CH₂-,
- i) CH₃O-NH-,
- j) (C₁-C₃)alkyl-O₂C-

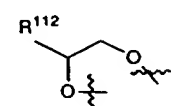
k) $\text{CH}_3\text{-C(O)-}$,

l) $\text{CH}_3\text{-C(O)-CH}_2\text{-}$,


m)  , or

n) 

A¹ and A² taken together are:

a) 

b) O= , or

c)  ;

wherein R¹⁰² is

a) H-,

b) $\text{CH}_3\text{-}$,

c) phenyl- $\text{CH}_2\text{-}$, or

d) $\text{CH}_3\text{C(O)-}$;

wherein R¹⁰³ is

a) (C₁-C₃)alkyl-, or

b) phenyl-;

wherein R¹⁰⁴ is

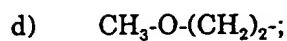
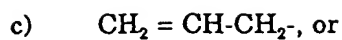
a) H-, or

b) HO-;

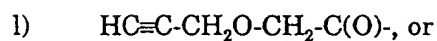
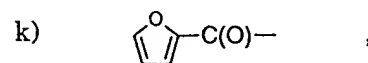
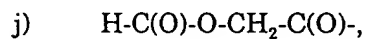
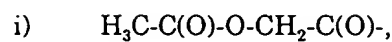
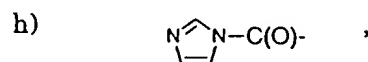
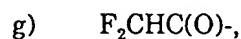
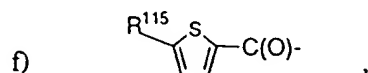
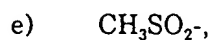
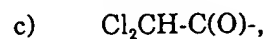
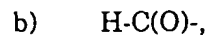
wherein R¹⁰⁵ is

a) H-,

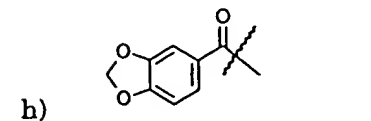
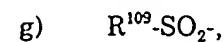
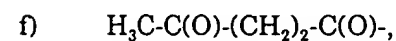
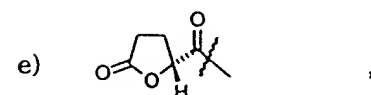
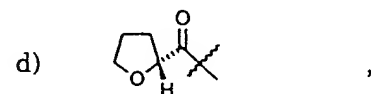
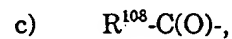
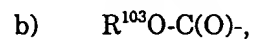
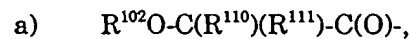
b) (C₁-C₃)alkyl-,



wherein R^{106} is



wherein R^{107} is



- i) $\text{HO-CH}_2\text{-C(O)-}$,
- j) $\text{R}^{116}\text{-(CH}_2\text{)}_2\text{-}$,
- k) $\text{R}^{113}\text{-C(O)-O-CH}_2\text{-C(O)-}$,
- l) $\text{(CH}_3\text{)}_2\text{N-CH}_2\text{-C(O)-NH-}$,
- m) $\text{NC-CH}_2\text{-}$,
- n) $\text{F}_2\text{-CH-CH}_2\text{-}$, or
- o) $\text{R}^{150}\text{R}^{151}\text{NSO}_2$

wherein R^{108} is

- a) H- ,
- b) $\text{(C}_1\text{-C}_4\text{)alkyl}$,
- c) $\text{aryl -(CH}_2\text{)}_p\text{-}$,
- d) $\text{ClH}_2\text{C-}$,
- e) $\text{Cl}_2\text{HC-}$,
- f) $\text{FH}_2\text{C-}$,
- g) $\text{F}_2\text{HC-}$,
- h) $\text{(C}_3\text{-C}_6\text{)cycloalkyl}$, or
- i) $\text{CNCH}_2\text{-}$.

wherein R^{109} is

- a) $\text{alkylC}_1\text{-C}_4\text{-}$,
- b) $\text{-CH}_2\text{Cl}$
- c) $\text{-CH}_2\text{CH=CH}_2\text{-}$,
- d) aryl , or
- e) $\text{-CH}_2\text{CN}$;

wherein R^{110} and R^{111} are independently

- a) H- ,
- b) $\text{CH}_3\text{-}$; or

wherein R^{112} is

- a) H- ,
- b) $\text{CH}_3\text{O-CH}_2\text{O-CH}_2\text{-}$, or
- c) $\text{HOCH}_2\text{-}$;

wherein R^{113} is

- a) $\text{CH}_3\text{-}$,
- b) $\text{HOCH}_2\text{-}$,
- c) $\text{(CH}_3\text{)}_2\text{N-phenyl}$, or
- d) $\text{(CH}_3\text{)}_2\text{N-CH}_2\text{-}$;

wherein R^{114} is

- a) HO-,
- b) CH_3O -,
- c) H_2N -,
- d) $CH_3O-C(O)-O$ -,
- e) $CH_3-C(O)-O-CH_2-C(O)-O$ -,
- f) phenyl- $CH_2-O-CH_2-C(O)-O$ -,
- g) $HO-(CH_2)_2-O$ -,
- h) $CH_3O-CH_2-O-(CH_2)_2-O$ -, or
- i) CH_3O-CH_2-O -, wherein R^{113} is

- a) CH_3 -,
- b) $HOCH_2$ -,
- c) $(CH_3)_2N$ -phenyl, or
- d) $(CH_3)_2N-CH_2$ -;

wherein R^{115} is

- a) H-, or
- b) Cl-;

wherein R^{116} is

- a) HO-
- b) CH_3O -, or
- c) F;

wherein R^{150} and R^{151} are each H or alkyl C_1-C_4 or R^{150} and R^{151} taken together with the nitrogen atom to which each is attached form a monocyclic heterocyclic ring having from 3 to 6 carbon atoms;

B is an unsaturated 4-atom linker having one nitrogen and three carbons;

M is

- a) H,
- b) C_{1-8} alkyl,
- c) C_{3-8} cycloalkyl,
- d) $-(CH_2)_mOR_{13}$, or
- e) $-(CH_2)_n-NR_{21}R_{22}$;

Z is

- a) O,
- b) S, or
- c) NM;

W is

- a) CH ,

- b) N, or
- c) S or O when Z is NM;

Y is

- a) H,
- b) F,
- c) Cl,
- d) Br,
- e) C₁₋₃ alkyl, or
- f) NO₂;

X is

- a) H,
- b) -CN,
- c) OR₂₇,
- d) halo,
- e) NO₂,
- f) tetrazoyl,
- g) -SH,
- h) -S(=O)_iR₄,
- i) -S(=O)₂-N=S(O)_jR₅R₆,
- j) -SC(=O)R₇,
- k) -C(=O)R₂₅,
- l) -C(=O)NR₂₇R₂₈,
- m) -C(=NR₂₉)R₂₅,
- n) -C(R₂₅)(R₂₈)-OR₁₃,
- o) -C(R₂₅)(R₂₈)-OC(=O)R₁₃,
- p) -C(R₂₈)(OR₁₃)-(CH₂)_h-NR₂₇R₂₈,
- q) -NR₂₇R₂₈,
- r) -N(R₂₇)C(=O)R₇,
- s) -N(R₂₇)-S(=O)_iR₇,
- t) -C(OR₁₄)(OR₁₅)R₂₈,
- u) -C(R₂₅)(R₁₆)-NR₂₇R₂₆, or
- v) C₁₋₈ alkyl substituted with one or more halos, OH, =O other than at alpha position, -S(=O)_iR₁₇, -NR₂₇R₂₈, C₂₋₅ alkenyl, C₂₋₅ alkynyl, or C₃₋₈ cycloalkyl;

R₄, R₅, R₆, R₇, R₁₃, R₁₄, R₁₅, R₁₆, and R₁₇ are the same as defined above;

R₂₅ is

- a) H,

- b) C_{1-8} alkyl optionally substituted with one or more halos, C_{3-8} cycloalkyl, C_{1-4} alkyl substituted with one or more of $-S(=O)_iR_{17}$, $-OR_{11}$, or $OC(=O)R_{13}$, $NR_{27}R_{28}$, or

- c) C_{2-5} alkenyl optionally substituted with CHO, or CO_2R_{13} ;

R_{26} is

- a) R_{28} , or
b) $NR_{27}N_{28}$;

R_{27} and R_{28} at each occurrence are the same or different and are

- a) H,
b) C_{1-8} alkyl,
c) C_{3-8} cycloalkyl,
d) $-(CH_2)_mOR_{13}$,
e) $-(CH_2)_h-NR_{21}R_{22}$, or
f) R_{27} and R_{28} taken together are $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_hCH(COR_7)-$, or $-(CH_2)_2N(CH_2)_2(R_7)$;

R_{29} is

- a) $-NR_{27}R_{28}$,
b) $-OR_{27}$, or
c) $-NHC(=O)R_{28}$;

wherein R_{30} is

- a) H,
b) C_{1-8} alkyl optionally substituted with one or more halos, or
c) C_{1-8} alkyl optionally substituted with one or more OH, or C_{1-6} alkoxy;

wherein E is

- a) NR_{39} ,
b) $-S(=O)_i$, or
c) O;

R_{38} is

- a) H,
b) C_{1-6} alkyl,
c) $-(CH_2)_q$ -aryl, or
d) halo;

R_{39} is

- a) H,
b) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,
c) $-(CH_2)_q$ -aryl,
d) $-CO_2R_{40}$,

- e) $-\text{COR}_{41}$,
- f) $-\text{C}(=\text{O})-(\text{CH}_2)_q-\text{C}(=\text{O})\text{R}_{40}$,
- g) $-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl,
- h) $-\text{S}(=\text{O})_2-(\text{CH}_2)_q$ -aryl, or
- i) $-(\text{C}=\text{O})_j$ -Het;

R_{40} is

- a) H,
- b) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,
- c) $-(\text{CH}_2)_q$ -aryl, or
- d) $-(\text{CH}_2)_q-\text{OR}_{42}$;

R_{41} is

- a) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,
- b) $-(\text{CH}_2)_q$ -aryl, or
- c) $-(\text{CH}_2)_q-\text{OR}_{42}$;

R_{42} is

- a) H,
- b) C_{1-6} alkyl,
- c) $-(\text{CH}_2)_q$ -aryl, or
- d) $-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl;

aryl is

- a) phenyl,
- b) pyridyl, or
- c) naphthyl; a to c optionally substituted with one or more halo, -CN, OH, SH, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} alkylthio;

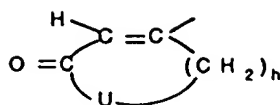
wherein R_{43} is

- a) H,
- b) C_{1-2} alkyl,
- c) F, or
- d) OH;

R_{44} is

- a) H,
- b) CF_3 ,
- c) C_{1-3} alkyl optionally substituted with one or more halo,
- d) phenyl optionally substituted with one or more halo,
- e) R_{44} and R_{45} taken together are a 5-, 6-, or 7-membered ring of the formula,

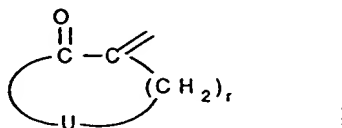
or



- f) R₄₄ and R₄₅ taken together are -(CH₂)_k-, when R₄₆ is an electron-withdrawing group;

R₄₅ and R₄₆ at each occurrence are the same or different and are

- an electron-withdrawing group,
- H,
- CF₃,
- C₁₋₃ alkyl optionally substituted with one halo,
- phenyl, provided at least one of R₄₅ or R₄₆ is an electron-withdrawing group, or
- R₄₅ and R₄₆ taken together are a 5-, 6-, 7-membered ring of the formula



U is

- CH₂,
- O,
- S, or
- NR₄₇;

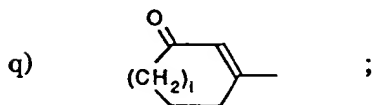
R₄₇ is

- H, or
- C₁₋₅ alkyl;

wherein R₄₈ is

- carboxyl,
- halo,
- CN,
- mercapto,
- formyl,
- CF₃,
- NO₂,

- h) C₁₋₆ alkoxy,
- i) C₁₋₆ alkoxycarbonyl,
- j) C₁₋₆ alkythio,
- k) C₁₋₆ acyl,
- l) -NR₄₉ R₅₀,
- m) C₁₋₆ alkyl optionally substituted with OH, C₁₋₅ alkoxy, C₁₋₅ acyl, or -NR₄₉R₅₀,
- n) C₂₋₈ alkenylphenyl optionally substituted with one or two R₅₁,
- o) phenyl optionally substituted with one or two R₅₁,
- p) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R₅₁, or



R₄₉ and R₅₀ at each occurrence are the same or different and are

- a) H,
- b) C₁₋₄ alkyl,
- c) C₅₋₆ cycloalkyl, or
- d) R₄₉ and R₅₀ taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, C₁₋₃ alkyl, or C₁₋₃ acyl;

R₅₁ is

- a) carboxyl,
- b) halo,
- c) -CN,
- d) mercapto,
- e) formyl,
- f) CF₃,
- g) -NO₂,
- h) C₁₋₆ alkoxy,
- i) C₁₋₆ alkoxycarbonyl,
- j) C₁₋₆ alkythio,
- k) C₁₋₆ acyl,

- l) C_{1-6} alkyl optionally substituted with OH, C_{1-6} alkoxy, C_{1-6} acyl, or $-NR_{49}R_{50}$,
- m) phenyl,
- n) $-C(=O)NR_{52}R_{53}$,
- o) $-NR_{49}R_{50}$,
- p) $-N(R_{52})(-SO_2R_{54})$,
- q) $-SO_2-NR_{52}R_{53}$, or
- r) $-S(=O)_iR_{54}$;

R_{52} and R_{53} at each occurrence are the same or different and are

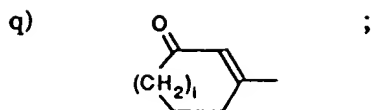
- a) H,
- b) C_{1-6} alkyl, or
- c) phenyl;

R_{54} is

- a) C_{1-4} alkyl, or
- b) phenyl optionally substituted with C_{1-4} alkyl;

wherein R_{55} is

- a) carboxyl,
- b) halo,
- c) $-CN$,
- d) mercapto,
- e) formyl,
- f) CF_3 ,
- g) $-NO_2$,
- h) C_{1-6} alkoxy,
- i) C_{1-6} alkoxycarbonyl,
- j) C_{1-6} alkythio
- k) C_{1-6} acyl,
- l) $-NR_{56}R_{57}$,
- m) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{56}R_{57}$,
- n) C_{2-8} alkenylphenyl optionally substituted with one or two R_{58} ,
- o) phenyl optionally substituted with one or two R_{58} ,
- p) a 5- or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{58} , or

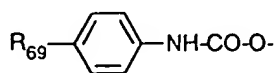


R₅₆ and R₅₇ at each occurrence are the same or different and are

- a) H,
- b) formyl,
- c) C₁₋₄ alkyl,
- d) C₁₋₄ acyl,
- e) phenyl,
- f) C₃₋₆ cycloalkyl, or
- g) R₅₆ and R₅₇ taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, phenyl, pyrimidyl, C₁₋₃ alkyl, or C₁₋₃ acyl;

R₅₈ is

- a) carboxyl,
- b) halo,
- c) -CN,
- d) mercapto,
- e) formyl,
- f) CF₃,
- g) -NO₂,
- h) C₁₋₆ alkoxy,
- i) C₁₋₆ alkoxy carbonyl,
- j) C₁₋₆ alkythio,
- k) C₁₋₆ acyl,
- l) phenyl,
- m) C₁₋₆ alkyl optionally substituted with OH, azido, C₁₋₅ alkoxy, C₁₋₅ acyl, -NR₆₅R₆₆, -SR₆₇, -O-SO₂R₆₈, or



- n) -C(=O)NR₆₉ R₆₀,
- o) -NR₆₆R₆₇,
- p) -N(R₆₉)(-SO₂R₆₄),

- q) $-\text{SO}_2-\text{NR}_{59}\text{R}_{60}$,
- r) $-\text{S}(=\text{O})_l\text{R}_{64}$,
- s) $-\text{CH}=\text{N}-\text{R}_{61}$, or
- t) $-\text{CH}(\text{OH})-\text{SO}_3\text{R}_{64}$;

R_{54} is the same as defined above;

R_{59} and R_{60} at each occurrence are the same or different and are

- a) H,
- b) C_{1-6} alkyl,
- c) phenyl, or
- d) tolyl;

R_{61} is

- a) OH,
- b) benzyloxy,
- c) $-\text{NH}-\text{C}(=\text{O})-\text{NH}_2$,
- d) $-\text{NH}-\text{C}(=\text{S})-\text{NH}_2$, or
- e) $-\text{NH}-\text{C}(=\text{NH})-\text{NR}_{62}\text{R}_{63}$;

R_{62} and R_{63} at each occurrence are the same or different and are

- a) H, or
- b) C_{1-4} alkyl optionally substituted with phenyl or pyridyl;

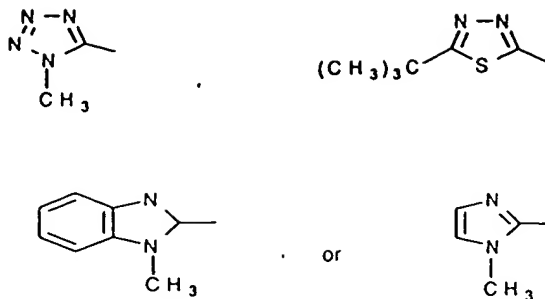
R_{64} is

- a) H, or
- b) a sodium ion;

R_{65} and R_{66} at each occurrence are the same or different and are

- a) H,
- b) formyl,
- c) C_{1-4} alkyl,
- d) C_{1-4} acyl,
- e) phenyl,
- f) C_{3-6} cycloalkyl,
- g) R_{65} and R_{66} taken together are a 5-, 6-membered saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with, including on the nitrogen atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl,
- h) $-\text{P}(\text{O})(\text{OR}_{70})(\text{OR}_{71})$, or
- i) $-\text{SO}_2-\text{R}_{72}$;

R₆₇ is



R₆₈ is C₁₋₃ alkyl;

R₆₉ is

- a) C₁₋₆ alkoxy carbonyl, or
- b) carboxyl;

R₇₀ and R₇₁ at each occurrence are the same or different and are

- a) H, or
- b) C₁₋₃ alkyl;

R₇₂ is

- a) methyl,
- b) phenyl, or
- c) tolyl;

wherein K is

- a) O, or
- b) S;

R₇₃, R₇₄, R₇₅, R₇₆, and R₇₇ at each occurrence are the same or different and are

- a) H,
- b) carboxyl,
- c) halo,
- d) -CN,
- e) mercapto,
- f) formyl,
- g) CF₃,

- h) $-\text{NO}_2$,
- i) C_{1-6} alkoxy,
- j) C_{1-6} alkoxy carbonyl,
- k) C_{1-6} alkythio,
- l) C_{1-6} acyl,
- m) $-\text{NR}_{78} \text{R}_{79}$,
- n) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, $-\text{NR}_{78} \text{R}_{79}$, $-\text{N}(\text{phenyl})(\text{CH}_2-\text{CH}_2-\text{OH})$, $-\text{O}-\text{CH}(\text{CH}_3)(\text{OCH}_2\text{CH}_3)$, or $-\text{O}-\text{phenyl}-[\text{para}-\text{NHC}(=\text{O})\text{CH}_3]$,
- o) C_{2-8} alkenylphenyl optionally substituted with R_{51} ,
- p) phenyl optionally substituted with R_{51} , or
- q) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with R_{51} ;

R_{51} is the same as defined above;

R_{78} and R_{79} at each occurrence are the same or different and are

- a) H,
- b) C_{1-4} alkyl,
- c) phenyl, or
- d) R_{78} and R_{79} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, C_{1-3} alkyl, or C_{1-3} acyl;

wherein T is

- a) O,
- b) S, or
- c) SO_2 ;

R_{75} , R_{76} , and R_{77} are the same as defined above;

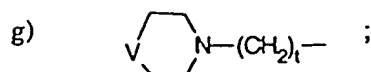
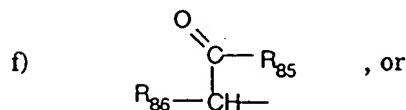
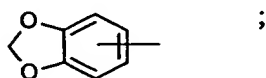
R_{80} is

- a) H,
- b) formyl,
- c) carboxyl,
- d) C_{1-6} alkoxy carbonyl,
- e) C_{1-8} alkyl,
- f) C_{2-8} alkenyl,

- wherein the substituents (e) and (f) can be optionally substituted with OH, halo, C₁₋₆ alkoxy, C₁₋₆ acyl, C₁₋₆ alkylthio or C₁₋₆ alkoxycarbonyl, or phenyl optionally substituted with halo,
- g) an aromatic moiety having 6 to 10 carbon atoms optionally substituted with carboxyl, halo, -CN, formyl, CF₃, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ acyl, C₁₋₆ alkylthio, or C₁₋₆ alkoxycarbonyl;
 - h) -NR₈₁R₈₂,
 - i) -OR₉₀,
 - j) -S(=O)_i-R₉₁,
 - k) -SO₂-N(R₉₂)(R₉₃), or
 - l) a radical of the following formulas:

R₈₁ and R₈₂ at each occurrence are the same or different and are

- a) H,
- b) C₃₋₆ cycloalkyl,
- c) phenyl,
- d) C₁₋₆ acyl,
- e) C₁₋₈ alkyl optionally substituted with OH, C₁₋₆ alkoxy which can be substituted with OH, a 5-, or 6-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, phenyl optionally substituted with OH, CF₃, halo, -NO₂, C₁₋₄ alkoxy, -NR₈₃R₈₄, or



V is

- a) O,

b) CH_2 , or

c) NR_{87} ;

R_{83} and R_{84} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl;

R_{85} is

a) OH,

b) C_{1-4} alkoxy, or

c) $-\text{NR}_{88} \text{R}_{89}$;

R_{86} is

a) H, or

b) C_{1-7} alkyl optionally substituted with indolyl, OH, mercaptyl, imidazolyl, methylthio, amino, phenyl optionally substituted with OH, $-\text{C}(=\text{O})-\text{NH}_2$, $-\text{CO}_2\text{H}$, or $-\text{C}(=\text{NH})-\text{NH}_2$;

R_{87} is

a) H,

b) phenyl, or

c) C_{1-6} alkyl optionally substituted by OH;

R_{88} and R_{89} at each occurrence are the same or different and are

a) H,

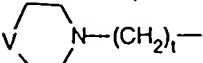
b) C_{1-5} alkyl

c) C_{3-6} cycloalkyl, or

d) phenyl;

R_{90} is

a) C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy or C_{1-6} hydroxy, C_{3-6} cycloalkyl, a 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three nitrogen atoms, which can in turn be substituted with one or two $-\text{NO}_2$, CF_3 , halo, $-\text{CN}$, OH, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl;

b) 

c) phenyl, or

d) pyridyl;

R₉₁ is

- a) C₁₋₁₆ alkyl,
- b) C₂₋₁₆ alkenyl,
wherein the substituents (a) and (b) can be optionally substituted with C₁₋₆ alkoxy carbonyl, or a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,
- c) an aromatic moiety having 6 to 10 carbon atoms, or
- d) a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,
wherein the substituents (c) and (d) can be optionally substituted with carboxyl, halo, -CN, formyl, CF₃, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ acyl, C₁₋₆ alkylthio, or C₁₋₆ alkoxy carbonyl;

R₉₂ and R₉₃ at each occurrence are the same or different and are

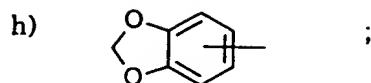
- a) H,
- b) phenyl,
- c) C₁₋₆ alkyl, or
- d) benzyl;

R₃₄ and R₃₅ at each occurrence are the same or different and are

- a) H,
- b) OH,
- c) C₁₋₆ alkyl optionally substituted with -NR₈₃ R₈₄, or
- d) R₃₄ and R₃₅ taken together are =O;

R₉₆ is

- a) an aromatic moiety having 6 to 10 carbon atoms,
- b) a 5-, or 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,
wherein the substituents (a) and (b) which can in turn be substituted with one or three -NO₂, CF₃, halo, -CN, OH, phenyl, C₁₋₅ alkyl, C₁₋₅ alkoxy, or C₁₋₅ acyl,
- c) morpholinyl,
- d) OH,
- e) C₁₋₆ alkoxy,
- f) -NR₈₃R₈₄,
- g) -C(=O)-R₉₇, or



R₉₇ is

- a) morpholinyl,
- b) OH, or
- c) C₁₋₆ alkoxy;

h is 1, 2, or 3;

i is 0, 1, or 2;

j is 0 or 1;

k is 3, 4, or 5;

l is 2 or 3;

m is 4 or 5;

n is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, 3, 4, or 5; with the proviso that n and p together are 1, 2, 3, 4, or 5;

q is 1, 2, 3, or 4;

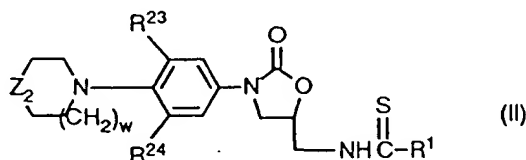
r is 2, 3, or 4;

t is 0, 1, 2, 3, 4, 5, or 6;

u is 1 or 2;

w is 0, 1, 2, or 3.

7. (Twice Amended) A method of treating [or preventing] osteoporosis[, or bone resorption[, or other bone disease characterized by the need to enhance bone formation] in a vertebrate mammal in need thereof comprising the administering to the vertebrate mammal an effective amount of a compound of formula II



wherein Z_2 is $-O_2S-$, $-O-$, $-N(R^{107})-$, $-OS-$, or $-S-$;

w is 0, 1, 2, or 3;

R^{23} and R^{24} are the same or different and can be H or F; and

R^1 is H, NH_2 , $NHalkylC_1-C_4$; $N(alkylC_1-C_4)_2$; $-N(CH_2)_{2-5}$;

$alkylC_1-C_4$; $OalkylC_1-C_4$; $SalkylC_1-C_4$; $alkylC_1-C_4$ substituted with 1-3F, 1-2Cl,

CN, or $-COOalkylC_1-C_4$, or $cycloalkylC_3-C_6$, wherein in each occurrence of the $alkyl$ group may be straight or branched; and

R^{107} is

- a) $R^{102}O-C(R^{110})(R^{111})-C(O)-$,
- b) $R^{103}O-C(O)-$,
- c) $R^{108}-C(O)-$,
- d) $R^{109}-SO_2-$,
- e) $NC-CH_2-$,
- f) $FCHCH_2-$, or
- g) $R^{150}R^{151}NSO_2-$;

wherein R^{102} is H, CH_3- , phenyl- CH_2- , or $CH_3C(O)-$; each of R^{110} and R^{111} is selected from H or CH_3 ; R^{103} is alkyl C_1-C_3 or phenyl; R^{108} is H, alkyl C_1-C_4 , aryl $(CH_2)_{0-5}$, $CNCH_2-$, $ClCH_2-$, Cl_2HC- , FH_2C- , F_2HC- , or cycloalkyl C_3-C_6 ; R^{150} and R^{151} are the same or different and are selected from H, alkyl C_1-C_4 , or R^{150} and R^{151} taken together with the nitrogen to which each is attached forms a monocyclic heterocyclic ring having from 3 to 6 carbon atoms.